REMARKS/ARGUMENTS

Applicants address the examiner's remarks in the order presented in the Office Action (dated August 26, 2004). All claim amendments are made without prejudice and do not represent an acquiescence in any ground of rejection.

STATUS OF THE CLAIMS

Claims 1, 10-14, 20 and 21 have been amended. Claim 13 was cancelled. After entry of this amendment, claims 1-12, 14, 20 and 21 will be pending. Support for the amendments to claims 1, 20 and 21 can be found throughout the application as filed. For example, support for the phrase "resensitization of HIV-1 to AZT" can be found at page 22, lines 1-5. Support for "HIV-1" and "AZT" can be found throughout the specification as filed. No new matter is added by this amendment.

Claims 1-14, 20, and 21 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

The examiner rejected the claims under 35 U.S.C. § 103(a) as unpatentable over several groupings of references:

Claims 1-3, 5-12, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996) and Kellam *et al.* (1992).

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ueno *et al.* (1995) and Kellam *et al.* (1992).

Claims 13 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996), as applied *supra* to claims 1-3, 5-12, 20, and 21, and further in view of Larder *et al.* (1999a, 1999b).

Claims 1-3, 5-12, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ekstrand *et al.* (1996) and Kellam *et al.* (1992).

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ueno *et al.* (1995) and Kellam *et al.* (1992).

Claims 13 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion et al. (1998) in view of Ekstrand et al. (1996) and Kellam et al. (1992) as applied *supra* to claims 1-3, 5-12, 20, and 21, and further in view of Larder et al. (1999a, 1999b).

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-14, 20, and 21 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants have amended the claims for greater clarity and consistency of claim language.

The examiner stated that Claims 1, 20, and 21 all include the phrase "the reaction products of substances" which, in the examiner's opinion, remained vague and indefinite. The examiner was of the opinion that the phrase was confusing since the skilled artisan would first add assay reagents (not reaction products) to the reaction well, followed by the enzyme of interest. Applicants have amended claims 1, 20 and 21 as suggested by the examiner making a bone fide attempt to address this rejection. Applicants welcomes any further guidance from the examiner if Applicants failed comply with the complete suggestion made by the examiner.

Claims 1, 20, and 21 were further rejected under 35 U.S.C. § 112, second paragraph, because the reference to various RT mutations (*e.g.*, M41L) was allegedly vague and indefinite. However, the examiner stated that by providing a reference isolate will enable the skilled artisan to accurately determine where the precise mutation is in any given enzyme (*i.e.*, wherein said mutant is selected from the group consisting of M41L/T215Y. . . wherein said numbering scheme is based upon the prototypical isolate HIV-1_{BH-10}). Applicants have amended claims 1, 20 and 21 as suggested by the examiner.

Claim 13 allegedly referenced a mutant containing mutations at codons 67, 69, and 70. The examiner stated that the parent claim failed to mention this combination of mutations. To expedite prosecution, Applicants have cancelled claim 13 without prejudice.

Claim 14 remained rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The examiner stated that the claim still referenced an "insertional mutation at nucleotide triplet encoding codon 69" which the examiner felt was vague and indefinite since the precise nature and location of the mutation was not clearly set forth. The examiner stated that the specification indicates drug-resistant forms of RT contain a single or multiple

amino acid insertion between codons 69 and 70 and suggested amending this claims to read "wherein the HIV-1 mutant RT enzyme contains an amino acid insertion between codons 69 and 70". Applicants have accepted the examiner's suggestion and have amended claim 14 accordingly.

Without acceding to the propriety of the rejection of pending claims 1-14, 20 and 21 under 35 U.S.C. § 112, second paragraph, Applicants respectfully request reconsideration of the claims as amended. For these reasons, Applicants request the examiner to withdraw the rejection of pending claims 1-14, 20 and 21 under 35 U.S.C. § 112, second paragraph.

REJECTIONS UNDER 35 UNDER 35 U.S.C. § 103

Claims 1-3, 5-12, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996) and Kellam *et al.* (1992). Applicants respectfully request withdrawal of the rejection because there are elements of the invention of the amended claims that the cited references neither teach nor suggest and because no motivation to combine the cited references has been established.

When applying 35 U.S.C. § 103, adherence to the following tenets of patent law is required: (a) the claimed invention must be considered as a whole; (b) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (d) reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); MPEP § 2141. Moreover, to avoid the pitfall of hindsight, the examiner must "identify ***specifically*** . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them," *In re Rouffet* 47 USPQ2d 1453, 1459 (Fed. Cir. 1998). Applicants respectfully submit that the required criteria set forth above has not been satisfied. Thus, a *prima facie* case of obviousness has not been set forth.

Claims 1, 20 and 21, as amended, are directed toward an HIV-1 RT assay to assess resensitization of HIV-1 to treatment with AZT. The claims now require a reaction well with the following components: (i) at least one template for an HIV RT enzyme; (ii) at least one primer; (iii) at least one detectable dNTP substrate; (iv) AZT; and (v) at least one

ribonucleotide chosen from ATP and GTP, or at least one pyrophosphate. Additional steps recite comparative steps involving both the wildtype and mutant RTs.

The examiner cites the Kellam reference as identifying mutant HIV-1 RTs that played a role in drug-resistance. Specifically, the examiner stated that Kellam identified mutant RTs carrying the mutations M41L and T215Y and their enzymatic activity ascertained (see Table 2, p. 1937) to bolster his position that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to employ the mutant RTs disclosed by Kellam *et al.* (1992) since these represent clinically important variants.

The Kellam reference, however, does not disclose at least the following specific elements of Applicants' claimed invention:

- a mutant selected from the group consisting of M41L / M184V / T215Y; M41L / D67N / K70R / M184V / T215Y; M41L / D67N / K70R / M184V / L210W / R211K / L214F / T215Y; T69S-SS; T69S-SG; T69S-AG; and T69S-SS / T215Y, wherein said numbering scheme is based upon the prototypical isolate HIV-1_{BH-10}

Given this deficiency, the rejection of claims 1, 20, and 21 for alleged obviousness under § 103(a) is improper and should be withdrawn. *In re Payne*, 203 U.S.P.Q. 245, 255 (C.C.P.A. 1979) (references relied upon to support rejection under § 103 must place the claimed invention in the possession of the public); *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974) (all limitations set forth in a patent claim must be taught or suggested in the prior art to establish a *prima facie* case of obviousness).

There is nothing in the Kellam reference that would motivate a skilled artisan to point to the particular mutants as now claimed by Applicants. Even if one were motivated to look elsewhere for the resensitization method (and Applicants are not conceding that such motivation exists), the Meyer or Ekstrand reference do not supply the missing elements (the specific mutants as claimed). Therefore the deficiency in Kellam is not remedied by the citation of either the Meyer or Ekstrand. The law requires that motivation come from a fair reading of all the references, rather than from combining only selected language from the prior art with the Applicants' disclosure. Moreover, the dependent claims further define the

invention. Certainly, none of the cited references suggest or motivate the particular combination claimed in the dependent claims.

Applicants assert that, in light of the limited applicability of the Kellam reference to employ the mutant RTs disclosed (since these represent clinically important variants), the examiner has impermissibly used hindsight reconstruction in arriving at the conclusion that the present invention is obvious. Because both the Meyer and the Kellam references are limited to applicability for determining the resensitization of HIV-1 to AZT as now claimed, there is no indication that the techniques described therein would be successful if used to determine the resensitization of HIV-1 to AZT. Accordingly, one skilled in the art would not be motivated to combine the teachings of the Kellam reference with the Meyer reference, together with Ekstrand, with an expectation of success to achieve the present invention. Thus, a *prima facie* case for obviousness has not been established.

To set forth a proper *prima facie* case of obviousness, it must be shown that one of skill would have derived from the combination of references a reasonable expectation of success in undertaking the claimed methods. The cited references, however, provide no reason for one to expect that the particular combination of mutants would be useful in an assay for determining resensitization of HIV-1 to AZT. None of the cited references even discuss the use of a mutant selected from the group consisting of M41L / M184V / T215Y; M41L / D67N / K70R / M184V / T215Y; M41L / D67N / K70R / M184V / L210W / R211K / L214F / T215Y; T69S-SS; T69S-SG; T69S-AG; and T69S-SS / T215Y, wherein said numbering scheme is based upon the prototypical isolate HIV-1_{BH-10}. Thus, the cited references, either alone or in combination would not have provided one of skill with the requisite reasonable expectation of success.

Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, rebuts *prima facie* obviousness. *In re Chupp*, 816 F.2d 643, 646, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987).

Applicants' methods provide surprising results, which are entirely unexpected in light of the disclosure of the cited references. It is well settled in the courts that greater than expected results are evidence of nonobviousness. See MPEP 716.02(a). A showing that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of significant practical advantage is sufficient to

overcome a *prima facie* case of obviousness. *Ex parte* The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991); see also *In re Chupp*, 816 F.2d 643, 646, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987). Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, rebuts *prima facie* obviousness. Applicants' virus with the 3TC mutation, M184V, in a background of AZT mutations, showed resensitization to AZT (5-6 fold). Further support can be found in the Specification at page 21 (Table 1) and at page 22, lines 1- 6.

Because there are elements of the invention of the amended claims that the cited references neither teach nor suggest and because one of ordinary skill in the art would not have been motivated to combine the cited references, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5-12, 20, and 21.

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ueno *et al.* (1995) and Kellam *et al.* (1992).

For the reasons set forth above, there is no motivation to combine the teachings of the Kellam reference with the Meyer and Ueno references. Accordingly, a *prima facie* case for obviousness has not been established, and applicants respectfully request withdrawal of the rejection of claim 4.

Claims 13 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996), as applied *supra* to claims 1-3, 5-12, 20, and 21, and further in view of Larder *et al.* (1999a, 1999b).

Without acceding to the propriety of the rejection of pending claims 13 and 14 under 35 U.S.C. § 103(a), Applicants respectfully request reconsideration of the claims as amended. Claim 13 was cancelled without prejudice and claim 14 was amended for greater clarity and consistency of claim language. More specifically, claim 14 is dependent on claim 1 which is now directed to determination of resensitization of HIV-1.

The examiner states that Larder et al. (1999a; 1999b) disclose that HIV-1 RT resistant variants carry mutations at amino acids 67, 69, and 70, and between amino acids 69 and 70. Together with the reasons set forth above, there is no motivation to combine the teachings of Meyer and Ekstrand with Larder references. Accordingly, a *prima facie* case for obviousness has not been established, and Applicants respectfully request withdrawal of the rejection of claim 13 and 14.

Claims 1-3, 5-12, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ekstrand *et al.* (1996) and Kellam *et al.* (1992).

For the reasons set forth above, there is no motivation to combine the teachings of the Kellam reference with the Meyer and Ueno references. The Kellam reference is deficient for the reasons stated above and these reasons are applicable here. Accordingly, a *prima facie* case for obviousness has not been established, and Applicants respectfully request withdrawal of the rejection of claim 1-3, 5-12, 20, and 21.

Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ueno *et al.* (1995) and Kellam *et al.* (1992).

For the reasons set forth above, there is no motivation to combine the teachings of the Kellam reference with the Arion and Ueno references. The Kellam reference is deficient for the reasons stated above and these reasons are applicable here. Accordingly, a *prima facie* case for obviousness has not been established, and Applicants respectfully request withdrawal of the rejection of claim 4.

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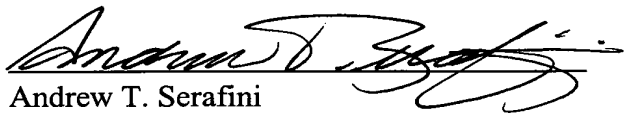
Without acceding to the propriety of the rejection of pending claims 13 and 14 under 35 U.S.C. § 103(a), Applicants respectfully request reconsideration of the claims as amended. Claim 13 was cancelled without prejudice and claim 14 was amended for greater clarity and consistency of claim language.

Together with the reasons set forth above, there is no motivation to combine the teachings of the Kellam reference with the Ekstrand, Arion, and Larder references. Accordingly, a *prima facie* case for obviousness has not been established, and Applicants respectfully request withdrawal of the rejection of claim 13 and 14.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submits that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Date: February 28, 2005



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